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RESPROGEN AND INFLUENZA VACCINES

Resprogen (Parke, Davis) is a new vaccine combining polyvalent influenza virus with adenovirus types 3, 4 and 7. It is the opinion of Medical Letter consultants that immunization of civilian populations against adenovirus infections is neither necessary nor desirable, and that this combined vaccine should not be substituted for immunization against influenza alone.

The effectiveness of a polyvalent influenza vaccine in reducing the frequency and severity of endemic and epidemic influenza is well established. The Public Health Service Advisory Committee on Influenza Research recently re-emphasized the great value of annual immunization of special-risk persons with such vaccines.

GROUPS REQUIRING INFLUENZA VACCINES - Routine immunization each fall is recommended for persons of all ages who suffer from chronic debilitating diseases, particularly patients with rheumatic heart disease, arteriosclerotic or hypertensive heart disease, cardiac insufficiency, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, pulmonary tuberculosis, diabetes mellitus and Addison's disease. Immunization is also recommended for pregnant women and for persons over 65. Influenza may not be more frequent in these special-risk groups, but the occurrence of influenza in such persons is more likely to be a life-threatening event.

The Public Health Service Advisory Committee recommends two subcutaneous injections separated by an interval of at least two months. The recommended dose for each injection is 1 cc. (500 CCA units). Each fall thereafter a single 1-cc. booster dose of the vaccine should be administered subcutaneously.

ADENOVIRUS VACCINES - As for adenovirus vaccines, their usefulness for the civilian population is not established. If adenovirus infections are confused with the common cold, costly and misdirected immunizations may become a fashion. There are some 23 distinct adenoviruses which produce acute respiratory disease (ARD), usually mild, and often associated with conjunctivitis. Of the three adenovirus types in Resprogen, infections with types 4 and 7 occur most frequently in military groups; there is no proof that they cause much illness in civilians. Though the third, type 3, may occasionally induce a severe respiratory infection in winter in adults or children, its effects are manifested chiefly in mild summer epidemics among children. Resprogen is recommended, how-

ever, only for adults over 16. Extensive field trials have indicated a high level of effectiveness for vaccines against adenoviruses 4 and 7 among military recruits; the effectiveness and duration of effect of type-3 virus vaccine for either military or civilian populations are still to be determined.

On the basis of all the evidence, Medical Letter consultants support the view of the Expert Committee on Respiratory Virus Disease of the World Health Organization (Report No. 170, 1959) that there is "...no real basis for general use of the [adenovirus] vaccine."

The cost of Resprogen to the physician is about $12 for 5 cc. Polyvalent influenza vaccine (500 CCA units) is available from many companies, and costs about $4 for 5 cc.

DRUG TREATMENT OF HYPERTHYROIDISM

The classical syndrome of severe hyperthyroidism is only occasionally encountered, but milder hyperthyroidism is common; in this condition, the results of therapy with antithyroid drugs are often gratifying and lasting. Many experienced physicians find that the drugs are worth trying even in patients with severe hyperthyroidism or toxic nodular goiter, though relapse is more frequent; if control proves difficult, or drug sensitization develops, radioactive iodine or surgery can be used. The antithyroid drugs may also be used in severely hyperthyroid patients before surgery or before radioactive iodine is administered.

DRUGS IN USE - Propylthiouracil USP, methimazole USP (Tapazole - Lilly), carbimazole BP (Neo-Mercazole - British Schering), potassium perchlorate, methylthiouracil USP (Muracil - Organon), and iothiouracil (Itrumil - Ciba) are among the drugs used both in the United States and abroad.

The interval between the beginning of therapy and therapeutic response may vary from a few days to many weeks. To assure continuous effect the compounds should be administered on a regular schedule, usually every eight hours around the clock. Where the hyperthyroidism is severe, the interval may occasionally have to be shortened to six or even four hours. The average dosage of the various compounds is as follows: propylthiouracil, methylthiouracil and iothiouracil - 300 mg. per day; methimazole and carbimazole - 30 to 60 mg. per day; potassium perchlorate - 600 to 1000 mg. per day.

TOXIC EFFECTS - Fewer than 10 per cent of patients experience toxic effects with the antithyroid drugs. Toxic reactions include drug fever, nausea, pruritus, rash, edema, conjunctivitis, salivary-gland enlargement and, rarely, thrombocytopenia, leukopenia and agranulocytosis. The patient should be cautioned to stop medication immediately if any reaction occurs, and to report to the physician for a white blood count (routine blood counts are not necessary or helpful). If a toxic reaction occurs with one drug, it is often possible to shift the patient to another in the group of drugs without a recurrence of the toxic reaction. Drug therapy must be stopped altogether, however, if the patient develops agranulocytosis.

There is no agreement that any one of the drugs is superior to the others either in effectiveness or in lack of toxicity, though most Medical Letter consultants start therapy with propylthiouracil or methimazole. Perchlorate has not been reported to cause agranulocytosis when taken at the dosage level of 600 mg. per day. However, at doses of 1000 mg. per day, not infrequently required for control of hyperthyroidism, agranulocytosis has been reported. One of the drugs, Itrumil, combines iodine with thiouracil, but the added iodine may confuse subsequent assays of thyroid function by radioactive iodine and by serum protein-bound iodine tests.

If any of the drugs are used in a pregnant patient with hyperthyroidism and the BMR is allowed to go below −5, the baby may be born with a goiter. If goiter does develop, however, it will soon regress without therapy. The drugs should not be administered to nursing mothers since they are secreted in the milk.

RADIOACTIVE IODINE - Radioactive-iodine therapy is now administered to adult patients in most medical centers, and it is generally very effective. Experience over 19 years has so far failed to support early fears that such therapy in the adult might be carcinogenic, or leukemogenic, or that it might interfere with reproduction. Some physicians treat patients of any age after adolescence with this isotope; many utilize it only in patients over forty years of age or in those below this age who have had previous thyroid surgery. Although there is no fetal thyroidal uptake of radioiodine until the beginning of the second trimester of pregnancy, it is now generally agreed that radioiodine therapy should not be given at any period of pregnancy.

Dosage of radioactive iodine is determined by the size of the goiter and the uptake of a tracer dose - about 2.5 to 20 millicuries. The full effect of a single dose is apparent only after two to six months. Second and third doses may be required in 15 to 20 per cent of the patients. A few patients may require a fourth dose. Myxedema occurs in about five per cent of patients on full doses of radioactive iodine; smaller doses lessen the problem of myxedema at the expense of a higher incidence of relapse and the need for a greater number of doses. The total cost to a patient of a single treatment ranges from $75 to as much as $400. The approximate cost of the two most commonly used drugs is as follows: propylthiouracil - $2 to $3 per hundred 50-mg. tablets (the daily cost of medication is 12¢ to 18¢); methimazole - $2 per hundred 5-mg. tablets at a cost of 12¢ a day. Potassium perchlorate is generally available only in powder form, but it can be made up into capsules or tablets by the pharmacist.

NICALEX

Nicalex (Walker), a combination of nicotinic acid and aluminum hydroxide, is promoted "for safer, more effective control of hypercholesterolemia." The comparison appears to be with ordinary nicotinic acid, and the effectiveness of 3- to 6-gram daily doses of nicotinic acid (not the amide) in reducing blood cholesterol has been well established. (See The Medical Letter, 2: 81, 1960 for a discussion of hypocholesterolemic agents and their effect on clinical atherosclerosis.) The use of nicotinic acid at such dosage levels has, however, been

discouraged by such common early side effects as flushing, itching and gastrointestinal irritation with pain, nausea, and vomiting. The manufacturer of Nicalex asserts that it is "hydrolyzed slowly and uniformly in the gastrointestinal tract into free nicotinic acid with aluminum hydroxide splitting off to provide an effective buffering action." By this mechanism, it is asserted, the unwanted side effects of ordinary nicotinic acid are eliminated.

EFFECTIVENESS AND SIDE EFFECTS - In the only published study cited by the manufacturer (W. B. Parsons, Jr., Current Therapeutic Res., 2:137, May 1960), Nicalex in equivalent doses appeared to be as effective as nicotinic acid in reducing elevated blood cholesterol levels. Contrary to the claim that "Nicalex has an almost complete absence of side effects," however, six of 14 patients in this study complained of flushing which was at least as bad as with similar doses of ordinary nicotinic acid; five reported a mild flush and only three reported no flush. There was no evidence that the combination drug caused less gastrointestinal disturbance than plain nicotinic acid. The author notes unpublished studies by other investigators showing fewer side effects, generally with smaller doses. In a subsequent study (JAMA, 173:1466, 1960), Dr. Parsons, who is one of the most active investigators of nicotinic acid therapy, reported seven cases of peptic ulcer appearing in patients taking ordinary nicotinic acid; since all the patients had severe emotional trauma before developing gastrointestinal symptoms, he points out, "nicotinic acid...may have played a minor role."

In a broader review of the subject (Am. J. Clin. Nutrition, 8:471, July-August, 1960), the same author pointed out that the cutaneous flush and itching which follow ingestion of ordinary nicotinic acid tend to disappear after the first week of treatment, with complete disappearance by the end of the second week in at least two-thirds of the patients. In about 10 per cent, the flush continued after every dose, although it was mild and did not interfere with treatment. Both skin and gastrointestinal side effects of nicotinic acid can be reduced if the drug is given during or immediately after a meal rather than on an empty stomach.

LONG-TERM EFFECTS - In Dr. Parsons' studies of nicotinic acid, the first two years of experience failed to show significant long-term effects; in the third year, however, evidence of liver toxicity appeared in some patients. Other observers have reported marked reduction of tolerance to glucose and even the appearance of frank diabetes. Blood uric acid levels have risen in some patients, although no instance of gout or renal calculi has been observed.

As pointed out previously in The Medical Letter (2:81, 1960), there is as yet no proof that reduction of blood cholesterol in patients with hypercholesterolemia or clinical atherosclerosis, or in patients with a bad family history of vascular disease, prevents or arrests the vascular disease. Nevertheless, many physicians feel that reduction of elevated cholesterol levels is a worthy aim. If the physician wants to try nicotinic acid, present evidence indicates that either the plain drug or Nicalex can be used with equal effectiveness. If there is a history of peptic ulcer, however, a buffered nicotinic acid preparation such as Nicalex may be preferred. The cost of Nicalex is about 7 or 8¢ per 625-mg. tablet. The equivalent amount of nicotinic acid (five 100-mg. tablets) costs about 3 to 5¢.

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